Odd genetic syndrome suggests increased blood vessel resistance could cause hypertension

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The culmination of two decades of research, a new study reveals the genetic causes of a curious, rare syndrome that manifests as hypertension (high blood pressure) accompanied by short fingers (brachydactyly type E). Six unrelated families with the syndrome come from across the globe - United States, Turkey, France, South America, and two from Canada - yet share mutations that cluster in a small region of phosphodiesterase 3A (PDE3A). Functional studies imply the mutations change resistance of blood vessels, an underappreciated mechanism for regulating blood pressure. The findings, published in *Nature Genetics*, suggest new directions for investigating causes of hypertension in the general population.

"Insights from this study could also lead to a new therapeutic strategy for heart failure - even in the overwhelming majority of patients with hypertension who don't have these mutations," says Matthew Movsesian, M.D., a cardiologist who studies PDE3. He and postdoctoral fellow Fabrice Vandeput, Ph.D., both from the Department of Internal Medicine at the University of Utah School of Medicine, collaborated with scientists from the Experimental and Clinical Research Center (ECRC) of the Charité Medical Faculty in Berlin, who led the multi-institutional study.

Hypertension has a well-documented link with diminished life expectancy and is a major risk factor for cardiovascular disease, the

most common cause of death worldwide. While genetic factors are known to play a role in hypertension, to date, only genes that regulate salt intake by the kidney have been associated with the condition, despite the fact that most people with hypertension are not sensitive to salt in their diet. The discrepancy suggests there are additional, unknown genes that influence hypertension.

To search for genes responsible for the disease, the German team focused for years on one extended Turkish family with the rare syndrome: hypertension and brachydactyly E (HTNB). Over time, they found five additional, unrelated families with the same, odd mixture of symptoms. Typically, affected individuals die of stroke before the age of 50 if the hypertension goes untreated.

The team discovered that each of the six families carries a different mutation that clusters within a small, five amino acid stretch of the PDE3A enzyme. Further, each alters PDE3's amino acid code. Biochemical experiments show these changes increase the enzyme's activity.

"This finding is too crazy to be made up," says Friedrich Luft, M.D., director of the ECRC and corresponding author on the study. "The mutations are astounding and that is what makes genetics fun."

Determining how the alterations influenced blood pressure was no easy task, partly because the enzyme resides in many cell types in the body. One clue lay in the observation that one of these is vascular smooth muscle cells (VSMCs), cells that line blood vessels. The scientists isolated mesenchymal stem cells from affected individuals and experimentally prompted them to become VSMCs. They observed that VSMCs carrying the mutation grew much more quickly than normal cells.

"If VSMCs are more dense, they would thicken the vessel walls and impair relaxation," explains Luft. "This could mean that PDE3A influences blood pressure by changing the resistance of blood vessels." The hypothesis remains to be verified in the affected families. Nevertheless, the results are the first implication that the increased PDE3 activity in VSMCs could be a cause of high blood pressure.

In addition to opening up new avenues for hypertension research, Movsesian believes the findings could lead to improving the design of PDE3 inhibitors, which are given to patients with advanced heart failure. Existing PDE3 inhibitors improve heart function by strengthening contractility, but have the unfortunate side effect of increasing risk for sudden cardiac death. Insights could stem from the paradoxical observation that patients with HTNB are protected from one of the typical consequences of hypertension, hypertrophy, the pathologic thickening of heart muscle.

"If we can understand how these more active forms of PDE3A protect the heart against the development of hypertrophy, we may gain an understanding how the reverse of that - PDE3 inhibition - increases sudden cardiac death," says Movsesian.

More information: The study will appear as "PDE3A mutations cause autosomal dominant hypertension with brachydactyly" in *Nature Genetics* online on May 11, 2015: nature.com/articles/doi:10.1038/ng.3302

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